The Can-ACT RFAs Preapplication Webinar (NOT-CA-22-123) (9/7/2022)
The Webinar Recording
Frequently Asked Questions

I. General questions

1. How many total grants will be awarded for the Can-ACT Network and how many for each mechanism between UG3/UH3 and U24?
   - A total of 7 UG3/UH3 grants and one U24 Coordinating Center (including both cycles) are anticipated to be awarded for the Can-ACT Network.

2. Do you anticipate 3-4 funded in the first cycle and 3-4 in the second?
   - In the first year (FY2023), based on our first-year budget, we expect to fund a total of 3 or 4 UG3/UH3 grants, ~2 for adult and ~2 for pediatric. But depending on the number/type of applications to be received and their merit, there can be more awards for adult solid tumors than for pediatric, or vice versa. An additional 3-4 UG3/UH3 awards will be made in the second year. The number of funded grants can change depending on the availability of funds.

3. Can an applicant submit a revised application if the first submission (October 2022 due date) will not get funded after review?
   - No, the applicant should submit a new application (A0) for the next June date if the first submission is not awarded. The new application can take the input from the first review but should be a new (A0) without reference to previous reviews.

4. If the UG3 phase were to produce negative findings after 2 years, could that make the UH3 invalid? Will a replacement UH3 be used?
   - The transition from UG3 to UH3 phase in the UG3/UH3 grants is based on successful completion of milestones and approval by the NCI administrative review. If a UG3 is not approved to transition to the UH3 phase, no replacement UH3 will be considered.

5. Can we look at an example of previously funded UG3/UH3 application with required clinical trials?
   - There are no specific examples of grants using UG3/UH3 mechanism for cell-based cancer immunotherapy to share with applicants.

6. Is it required to get IND approval from the FDA at the end of UG3 phase?
   - An IND approval from the FDA is required for initiating the clinical trial in the UH3 phase, which should start within the first year of UH3 phase. While IND approval may not happen at the end of UG3 phase, it should be done in the first year of UH3 phase so that the trial can start within the first year.

7. Who holds the IND for a multi-site trial, the ICN Core or the PI?
   - The grantee or grantee's institution will be responsible for filing and holing the IND; the ICN Core could provide guidance and review of materials for IND submission to the FDA.

II. ICN Core resource and multi-sites trials

1. Can the PI request ICN Core resources (e.g., cell manufacturing) during the UG3 phase?
   - Yes, the ICN Core resources can support a multi-site trial proposed in the UH3 phase.

2. How many core resources can be used in Frederick (FNLCR)?
   - Can-ACT members can access multiple ICN-Core (FNLCR) resources.

3. How many of the core Frederick resources available to the Can-ACT Network?
   - ICN Core resources are grouped into three (3) categories:
     (1) cGMP manufacturing for multi-site trials, including viral vectors and engineered cells
     (2) Product evaluation, including the development, standardization, and technology transfer of assays for cell therapy products
     (3) Quality systems oversight, including evaluation and guidance on GCP, GMP, and regulatory affairs compliance
   - Specific resources can be requested within these categories.

4. Are GMP facilities at FNLCR available to applicants who do not get the UG3/UH3 Can-ACT award?
   - The GMP facilities and resources at FNLCR are also available to investigators through a successful competitive application to the NCI Experimental Therapeutics Program (NExT, https://next.cancer.gov/).

5. Besides lentivirus and retro-virus vectors currently ICN Core uses, does the Core support other viruses such as herpes virus for GMP production?
   - The ICN Core has experience with producing clinical-grade herpesvirus and can support such requests. Novel viral vectors will require assessment for feasibility of production and process development.

6. How does ICN Core assist with regulatory compliance, particularly for CRISPR which has higher regulatory challenges?
   - The ICN core leverages its internal expertise in biopharmaceutical regulatory affairs, compliance with cGMP, and interactions with FDA to address and overcome hurdles to novel biopharmaceutical development and production.

7. Is ICN Core able or planning to do manufacturing of non-PBMC derived cell products such as TILs or iPSC-derived cells?
   - ICN Core does not currently have experience in non-PBMC derived cell products but can develop and adopt new platforms as the need arises and as feasibility allows.

8. Does the technology transfer from the extramural institution to the ICN Core (FNLCR) require percent effort from the PI? Is significant time expected from the PI?
   - Typically, 1-hour project team meetings are held on a regular basis, e.g., monthly or ad hoc, to discuss progress and needs with the technical expertise from the PI laboratory. The PI is considered part of the project team and encouraged to attend the project team meetings.

9. For a multi-center trial, will the cell manufacturing be done at the ICN Core or at the funded site? Does the UH3 funding cover both clinical trial and cell manufacturing or only the clinical trial and the ICN Core cover the cell manufacturing?
   - Cell manufacturing for a multi-center trial may be performed either at the funded site or by the ICN Core. If manufactured at the funded site then the cost needs to be budgeted in the grant application; if manufactured at the ICN Core, the ICN core provides these product as “in kind” contribution and the cost is not budgeted in the grant application.

10. Does the UH3 component have to use the NCI shared resource and does that need to be explicitly detailed in the application?
    - It is not a requirement for the UH3 phase to utilize the ICN Core resources. Planned use of the ICN Core needs to be described in adequate detail for reviewers' understanding.

11. Does the proposed clinical trial have to be multi-center from the beginning (first patient) to be eligible for use of the ICN Core, or can additional sites be added after the dose escalation phase (or first cohort of patients)?
    - To be eligible for use of the ICN Core cGMP production resources, the clinical trial may be *initiated* at a single site but there must be a written plan for expansion into a multi-site trial with letters of commitment from the additional sites.

12. Does the ICN Core take on new vectors/TCRs and if so how does the PI incorporate this into the application?
    - The ICN Core can establish capability for producing new vectors/TCRs in collaboration with the applicant in the UG3 phase, as described in the application, but the UH3 phase must contain a multi-site clinical trial (also see #11). The applicant should provide a plan for technology transfer of the new vectors/TCR to the ICN core as one of the milestones of the UG3 phase.

13. What happens if UG3 does not approve the manufacturing or the timeline to IND approval does not align with the start of UH3?
    - If the UG3 does not meet the project milestones, then it will not progress to the UH3 phase. While IND activation may not be synchronous with the start of the UH3 phase, it is assumed that delays e.g., FDA Clinical Hold issues will be resolved in a timely manner to allow the IND to proceed.

14. Does the ICN Core resource include the cost of product shipment?
    - Yes, shipping logistics are included in the ICN Core resource.

15. Is the ICN Core in kind support in GMP manufacturing (both virus and cells) not available to single site trials, which are more common than multi-site trials for phase 1? (If it has to be multi-site for use of the ICN Core, then that's a nonstarter for phase 1/early-stage studies)?
    - ICN Core cGMP production resources are only available to support multi-site trials; the facility is currently supporting two (2) multi-site early phase CAR-T cell therapy trials.

16. Can the PI leverage the ICN Core for lentiviral vector manufacturing if the PI plans to do only a single-site trial using on-site CAR-T manufacturing?
    - No, vector production is considered cGMP manufacturing and is only available to support multi-site trials. However, vector production by the FNLCR facility can be requested through the NCI Experimental Therapeutics Program (NExT, https://next.cancer.gov/).

17. Can the UG3 phase be a single site and UH3 be multi-sites and still get the ICN Core support (cell/vector production)?
    - Yes.

18. How will the logistics work if the PI proposes a research goal of improving the manufacturing of cells? Will this aim be incorporated into the ICN process for the UH3 phase?

- If the UH3 phase includes a multi-site trial AND the applicant intends to leverage the ICN Core for cGMP manufacturing, then the UG3 phase can include a plan to collaborate with the ICN Core for technology transfer/development of the improved manufacturing process (also see #s 11 & 12).

III. Research scope of Can-ACT

1. Can you clarify what the "objectives" in the UG3 portion mean in relation to the specific aims?
   - The UG3 phase must address at least 2 discrete but connected scientific *objectives* that will advance a new cell therapy concept to clinical testing and advance the understanding and/or success of treating solid tumors with adoptive cell therapy. Each objective may have one or more specific aims or sub-aims that can be accomplished within the 2-year timeline of the UG3 phase. Objectives in the UG3 portion need to include milestones. Examples of single objectives are listed in the relevant RFA.

2. Would the UH3 phase be required to have two different clinical trials or a single trial to test two ideas similar to the two objectives required in the UG3 phase?
   - No, only one clinical trial of one cellular product is required for the UH3 phase.

3. Would exploration of novel target antigens as one of the objectives in the UG3 phase be considered responsive?
   - Yes, as long as the new targeting can be advanced to IND enabling studies during the UG3 phase to initiate an early clinical trial in UH3.

4. While "animal model development" is listed as non-responsive to the RFAs, is it allowed to have animal model development that facilitates the IND enabling toxicity studies?
   - If the preclinical animal model is for the purpose of IND enabling studies to assess appropriate PD, PK and toxicity of a cellular product, the animal model development is allowed. This should be clearly documented as a milestone and be completed within the time frame of the UG3 to support a successful IND submission and commencement of a clinical trial in the first year of the UH3.

5. Are syngeneic animal studies considered "non-responsive" or appropriate?
   - Syngeneic model would be considered responsive only if it is needed to support a successful IND application.

6. Can the UG3/UH3 grant propose the use of patented CAR-T cells for the study?
   - Yes, a patented, FDA-approved CAR-T product can be proposed for further improvement/modification and in trials designed to use other therapeutic methods to modify the TME in the expansion of a new solid tumor therapeutic indication. Patented CAR-T cells that are not FDA approved and are being explored for the treatment of solid tumors is permitted and will be assessed by the review committee for scientific merit and innovation. (see review criteria in the RFA)

7. Does the proposed clinical trial have to be finished within the UH3 phase or it just needs to start at the UH3 phase?
   - Yes. The UH3 phase will initiate an early phase clinical trial within the first year and there should be milestones for every year in the UH3 phase for evaluation. It is expected that a small trial

would be completed in the UH3 phase, but long term follow up is out of scope of for this funding opportunity and is not within the budget of Can-ACT.

8. Do you have recommendations for budgeting for long term follow up for clinical trial patients beyond the term of the grant?
   - No, we don't have plans or budgets for long term follow up monitoring for clinical trial patients beyond the UG3/UH3 grants.

9. How critical is it to propose correlative studies as the time and budget considerations may not allow extensive correlative studies beyond some of the standard studies?
   - The correlative studies are a critical component of the UH3 phase, but the scope of the studies should be justified within the 3-year timeline and budget of the UH3. Supplemental funds may be pursued as needed to expand the correlative studies.

IV. Roles of the U24 Coordinating Center

1. What is the role of the U24 CC in assisting the use of the ICN Core? Will a direct interaction between the clinical center and the ICN be more efficient (e.g., receiving patient materials and shipping cell products)?
   - The U24 CC provides both scientific coordination and administrative support to the Can-ACT Network, including organizing a steering committee that involves the ICN Core, providing leadership and coordinating plans among the Network members including the ICN Core. It is expected and would be more effective that the clinical site will directly contact the U24 CC first and then coordinate the activities with the ICN Core.

2. Do the correlative studies have to go to the U24 Coordinating Center? In a multi-site study, can all the correlatives go to one (clinical) center so that it'll be one set of assays for consistency?
   - The U24 CC will develop and implement a governance strategy for shared data use and will develop and maintain a public-facing website for Can-ACT, but will not house preclinical or clinical data. The data repository and other data access and sharing functions will be further defined and announced to the Can-ACT awardees. Correlative studies may be done at one clinical site for consistency and the data sharing plan should address the management of the data.

3. Will the data analysis component (e.g., biomarker, imaging analysis, clinical trial monitoring) reside in the U24 Coordinating Center or should it be provided in the UG3/UH3 application?
   - No, the individual UG3/UH3 awardees should have data analysis component as appropriate for their proposed preclinical and clinical studies. The U24 Center is responsible for developing and implementing a governance strategy for shared data use and develop a strategy to define critical data elements and minimal data collection requirements, etc.

4. Are biostatistics and bioinformatics analysis functions considered a key component of the U24?
   - Yes, the U24 Center is responsible for developing and implementing a governance strategy for shared data use and providing bioinformatics and statistical support for the Can-ACT projects.

V. Applicant's eligibility and efforts

1. Can an early-stage investigators (ESIs) apply for the UG3/UH3 grant? Are there any implications of being an ESI?
   - ESIs are eligible for applying but need to fulfill the necessary requirements related with operation of the UG3/UH3 center. Applications deemed to have the highest scientific and technical merit will be discussed and assigned an overall impact score. Applications will NOT be percentiled and those from ESIs will be subjected to similar paylines as for established investigators.

2. For MPI applications, is it expected to have one translational PI for UG3 and one clinical PI for UH3?
   - For the UG3/UH3 applications, a single PI is eligible to conduct both UG3 and UH3 phases and there is no requirement for MPIs to have one translational PI for UG3 and one clinical PI for UH3. A single PI or MPIs will be evaluated for their expertise and experiences to lead the cell therapy preclinical development and clinical trials.

3. Can a PhD-PI leading the IND-enabling study (UG3) and an MD-PI leading a clinical trial (UH3) justify for an MPI application, or is a Department Chair (MD level) required to serve as an overall PI?
   - Yes, a PhD PI and an MD PI can lead the UG3 and UH3 phase, respectively. The PI doesn't have to be a MD level Department Chair.

4. Can U24 application include MPIs from a different institution?
   - Yes, MPIs from different institutions are allowed, but the consideration should be considered regarding the resources at different institutions and coordination among them to allow for effective operations of the U24 Center.

5. If two MPIs are involved in the grant, can the two PIs propose a single budget for both the UG3 and UH3 phases, or must their roles and budgets be confined to their own UG3 or UH3 component?
   - The two PIs can have budgets in both the UG3 and UH3 portions to allow inputs from one PI to the other leading PI in either the UG3 or UH3 phase.

6. Can the PI of the UG3/UH3 grant be a co-investigator of the U24 Coordinating Center?
   - Yes, serving as PI of one UG3/UH3 grant does not prevent the PI from serving as a PI/co-Investigator in the U24 Coordinating Center.

VI. Review of Can-ACT grants

1. Can one submit two applications with the same UG3 but different UH3 aims?
   - Each application will be judged for its scientific and technical merits. Applications for pediatric and adult solid tumors are responsive to separate RFAs. The PI should address any overlap when submitting two applications in the same review cycle. Two applications using the same UG3 component and different UH3 aims for one RFA to the same institution will not be awarded. Such two applications may be judged as substantially overlapping and one of the two would be administratively withdrawn without proceeding to peer review.

2. Are the reviewers encouraged to review the clinical feasibility of the models because the UG3 phase will transition to the UH3 phase?
   - Yes, the clinical feasibility of the UG3 component is part of the review criteria and its transition into the UH3 phase will be judged based on the feasibility and the quantitative milestones to be met in the UG3 phase.

3. Will multi-center trials, which can use the ICN Core resource, be prioritized during the peer review or programmatic reviews?
   - There is no single vs multi-centered trial prioritization during the scientific and technical review process. Only applications that are deemed meritorious will undergo a second level NCI programmatic review where prioritization for a multi-centered trial may be considered.

4. For new target antigens in the UG3 phase, would the information in the literature, or knowledge of biological mechanisms, be considered as sufficient preliminary data for the application? Or are specific data related to new target antigens required for the application to be considered?
   - A strong scientific foundation for the proposed new target is highly recommended for the UG3 phase (e.g., rigorous evidence from literature and/or the applicant's own preliminary data). Remember that new targets will need the necessary validation for IND submission and these milestones should be outlined with a plan to be able to move to a clinical trial in the first year of the UH3 phase.

VII. Involvement of NIH intramural and other federal scientists

1. Can the NIH intramural and the extramural PIs jointly apply for this grant mechanism?
   - In general, the NIH intramural scientists cannot serve as a PI in an extramural grant application. However, they may serve in a certain capacity (co-I, collaborator, etc.) in an extramural grant application to provide consultation without budget allocation. But this decision is best left to the Scientific Director of the NIH institute of the intramural scientist involved in the grant as there may be IC level restrictions. Please see the link for additional details: https://oir.nih.gov/sourcebook/ethical-conduct/research-ethics/nih-policies/intramural-extramural-collaborations.

2. Can an NIH intramural investigator be a multi-PI for the UH3 component (while an academic PI for the UG3 phase)?
   - NIH intramural investigators may not serve as MPIs for either UG3 or UH3 component as NIH cannot be the recipient institution for extramural funding. Depending on the extent of your planned involvement on an NIH extramural grant or cooperative agreement, you may need to get approval from your intramural IC Scientific Director.

3. Are there any issues with including a VA site in the multi-site trial?
   - VA sites are eligible to participate in these RFAs. As VA investigators and sites are part of a federal agency, there are budgetary factors that should be addressed in the justification section of the application.

VIII. Eligibility of and collaboration with small companies

1. Can PI(s) collaborate with small biotech companies for the UG3/UG3 projects?
   - Yes, small businesses are eligible to apply for the grant.

2. Are small companies eligible or encouraged to apply?
   - Yes, small businesses are eligible to apply for the grant. They are encouraged to collaborate with academic centers to manage the complex projects involving many aspects of preclinical and clinical studies and coordination.

3. Does the clinical PI (for the UH3 phase) need to have experiences in adoptive cell therapy trials or does experience in running other types of clinical trials suffice?
   - The clinical PI for the UH3 component is expected to have experience in early phase immuno-oncology clinical trials. The applicant will need to provide evidence that the assembled team has the technical and clinical expertise to conduct an immune cell therapy trial.

4. What background or experience is required of the PI of the U24 Coordinating Center? Is it mainly the biostatistics/bioinformatics? Does the PI need experience in solid tumor CAR-T data analyses or need support letters from collaborators who have done solid tumor CAR-T trials?
   - The PI for the U24 Coordinating Center should have strong experiences in running complex networks regardless of his/her background in biostatistics/bioinformatics or in cellular immunotherapies. However, the U24 team members should have sufficient expertise in immuno-oncology/cell-based therapies to contribute to the successful management of the U24 activities for the Can-ACT Network.

IX. IP issues from the Can-ACT

1. Does the intellectual property to be generated by Can-ACT go to the applicant as per the Bayh-Dole act? Are there any issues related to IP for which the PI needs to be aware of?
   - Yes, the IP generated by individual awardees from the Can-ACT during the grant period belongs to the grantee's institution.

2. Will the reviewers look at whether the investigators have freedom to operate and own the IP to the technology (e.g., the CAR/TCR construct)?
   - Yes, during the peer review, owning a patent and the freedom to operate around the IP will be evaluated by reviewers as part of the feasibility and innovation that would impact the overall score.